JACC Vol. 26, No. 7
December 1995:1637–42

Recombinant Hirudin (HBW 023) Prevents Troponin T Release After Coronary Angioplasty in Patients With Unstable Angina

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Objectives. **This study was performed to evaluate the efficacy of peri-interventional treatment with recombinant hirudin (r-hirudin [HBW 023]) compared with heparin in the prevention of troponin T release in patients with unstable angina.**

Background. **Percutaneous transluminal coronary angioplasty in patients with unstable angina is associated with a high risk of acute thrombotic complications.**

Methods. **Serial troponin T measurements were performed in 61 patients with unstable angina during the 48-h observation period after coronary angioplasty of the ischemia-related lesion. Patients were randomly assigned to peri-interventional intravenous treatment with either r-hirudin (dosage group I: 0.3-mg/kg body weight bolus, 0.12 mg/kg per h for 24 h; dosage group II: 0.5-mg/kg bolus, 0.24 mg/kg per h for 24 h) or heparin (150-IU/kg bolus, 20 IU/kg per h for 24 h). All patients received acetylsalicylic acid before coronary angiography. After 24 h, patients received a constant low dose infusion of either hirudin (0.04 mg/kg per h) or heparin (7 IU/kg per h) for another 24 h. The power of the study to detect a decrease in abnormal troponin T levels from 60% (heparin group) to 20% (combined r-hirudin groups) was 88%.**

Results. **Serial troponin T measurements revealed two peaks within the 48 h after coronary angioplasty in the heparin but not the hirudin groups. An elevated serum troponin T concentration (>0.2 ng/ml) within 48 h of coronary angioplasty was found in 9 (24%) of 38 patients in the hirudin groups (5 [25%] of 20 in dosage group I; 4 [22%] of 18 in dosage group II) compared with 11 (58%) of 19 in the heparin group ($p = 0.01$). We observed major cardiac events (death, myocardial infarction, abrupt vessel closure) in 1 (4.8%) of 21 patients in dosage group I, 1 (5.3%) of 19 in dosage group II and 3 (14.3%) of 21 in the heparin group ($p = 0.33$).**

Conclusions. **In this pilot trial, hirudin appears to be superior to heparin in preventing troponin T release after coronary angioplasty.**

(J Am Coll Cardiol 1995;26:1637–42)

Plaque rupture and subsequent thrombus formation have been shown (1–6) to play a fundamental role in the pathogenesis of unstable angina. In this subgroup of patients, percutaneous transluminal coronary angioplasty is associated with a marked risk of acute thrombotic complications as a result of extension of the underlying plaque rupture and further endothelial injury with augmented platelet activity, increased clotting activity and attendant spasm (7–14). The risk of acute vessel occlusion in these patients is thought to depend primarily on the extent of dissection and thrombin generation at the site of the lesion. Thrombin not only plays a key role within the clotting system, but is also the most potent and physiologically important activator of platelets.

The incidence of acute complications has been reduced by the use of heparin and acetylsalicylic acid (aspirin) before, during and after coronary angioplasty (15–17). However, there is strong evidence (18) that heparin and aspirin may not completely prevent coagulation activation during coronary angioplasty. Hirudin, a highly specific and direct inhibitor of thrombin, has been shown to be highly effective in preventing arterial thrombosis in animal (19–23) and human studies (24–26). It has therefore been postulated that hirudin might counteract coagulation activation and reduce ischemic events in patients undergoing coronary angioplasty for unstable angina. Because of its high sensitivity and specificity, troponin T has been used to detect myocardial cell injury (27).

Methods

Patients. Patients with a clinical diagnosis of unstable angina pectoris were eligible for inclusion in this multicenter trial,

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Manuscript received February 3, 1995; revised manuscript received June 1, 1995, accepted July 13, 1995.

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0735-1097/95/$9.50
0735-1097(95)00371-A

provided that the following criteria were met: 1) angina at rest, recent onset angina (≤4 weeks), postinfarction angina (≤4 weeks) or prolonged (≥10 min) or recurrent angina (at least two episodes lasting ≥5 min in any 1 day); 2) last attack of chest pain within the preceding 48 h; 3) at least one stenosis with a diameter reduction of at least 70% in any major coronary artery (right, left circumflex or left anterior descending or any side branch >2 mm in diameter) that was considered to be responsible for clinical symptoms and suitable for coronary angioplasty. Reasons for exclusion were >75 years old, body weight >100 kg, known abuse of alcohol or drugs and known hypersensitivity to contrast media or trial drugs, as well as acute myocardial infarction, thrombolytic therapy within the preceding week, hemodynamic instability, bleeding disorders or conditions predisposing to bleeding, history of intracranial aneurysm or stroke, uncontrolled hypertension (>180/100 mm Hg), serum creatinine levels >133 μmol/liter or other relevant and serious diseases. Ethical approval was obtained before start of the study, and informed written consent was obtained from all patients.

Study protocol. The study was designed as an open, heparin-controlled, randomized, multicenter trial. Two doses of recombinant hirudin (r-hirudin) were sequentially investigated. Within each dose group, patients were randomized to the two treatments (heparin or r-hirudin), with an overall ratio of 1:2.

In patients who received continuous intravenous heparin, the infusion was stopped before arterial puncture. Patients without premedication with aspirin received 500 mg of aspirin before coronary angiography. All patients were given an intracoronary bolus injection of 0.1 to 0.3 mg of nitroglycerin before coronary angiography. Immediately before coronary angioplasty, an intravenous bolus of either r-hirudin or heparin was given according to randomization. Thereafter, a constant infusion of r-hirudin or heparin was started and continued for 24 h.

After 22 to 26 h, repeat coronary angiography was performed to document the early result of coronary angioplasty. Two to three hours after the end of the control angiography, the arterial sheath was removed. A low dose infusion of the trial medication (r-hirudin or heparin) was subsequently instilled for another 24 h to prevent thromboembolism during the period of bed rest; aspirin was continued in a dosage of 100 to 300 mg/day.

Study medication. *Recombinant hirudin.* Recombinant hirudin (HBW 023, Behringwerke AG, Marburg, Germany) was administered intravenously in two different dose regimens: DOSE GROUP I = 0.3-mg/kg body weight bolus, followed by a constant 24-h infusion of 0.12 mg/kg per h. The goal was twofold to fourfold prolongation of the reference activated partial thromboplastin time. DOSE GROUP II = 0.5-mg/kg bolus, followed by a constant 24-h infusion of 0.24 mg/kg per h. The aim was to attain a twofold to fivefold prolongation of the reference activated partial thromboplastin time.

An additional bolus of either 0.3 or 0.5 mg/kg (depending on the dose group) was given when the activated partial thromboplastin time failed to reach the target range. If the activated partial thromboplastin time exceeded the upper limit of the target range, the infusion was interrupted for 2 h. After 24 h (end of the trial infusion), patients received a constant 24-h infusion of 0.04 mg/kg per h (both dose groups).

Heparin group. Patients received an intravenous bolus of 150 IU/kg of unfractionated heparin (Liquemin, Hoffmann LaRoche, Basle, Switzerland), followed by a constant 24-h intravenous infusion of 20 IU/kg per h. The activated partial thromboplastin time was adjusted to a twofold to fourfold prolongation of the reference value. After 24 h (end of the trial infusion), patients received a constant 24-h infusion of 7 IU/kg per h.

For patients who did not receive heparin before intervention, the patient's own baseline activated partial thromboplastin time was taken as the reference value in all treatment groups. For patients who were receiving heparin, the median activated partial thromboplastin time of the normal range was used.

Coronary angiography and coronary angioplasty. Coronary angiography and coronary angioplasty were performed using routine techniques through the femoral route. The cineangiograms were evaluated at the central core angiographic laboratory of the Medical Clinic II of the University of Mainz. All angiograms were stored on 35-mm cinefilm at 25 to

Table 1. Patient and Lesion Characteristics

	r-Hirudin		
	Dosage Group I (n = 21)	Dosage Group II (n = 19)	Heparin Group (n = 21)
Male/female	18/3	15/4	14/7
Age (yr)	58 ± 8	61 ± 9	60 ± 10
Time from onset of last episode of chest pain to start of treatment (h)	23.0 ± 14.0	22.7 ± 13.2	20.5 ± 14.3
Time from start of treatment to change to low dose infusion (h)	21.7 ± 6.8	23.6 ± 4.6	21.6 ± 7.1
No. of stenoses treated	23	25	22
Multivessel disease	11	7	5
Location of stenosis			
LAD	14	13	17
RCA	3	4	3
LCx	6	8	2
Diameter stenosis before coronary angioplasty	78.7 ± 7.8	79.6 ± 9.7	80.9 ± 9.8
Diameter stenosis after coronary angioplasty	33.1 ± 9.3	34.2 ± 10.7	35.1 ± 9.4
Acute angiographic success	20/20	19/19	18/20
Diameter stenosis after 24 h	39.0 ± 11.6	39.1 ± 13.0	41.6 ± 8.8
Thrombus before coronary angioplasty	10	10	10
Thrombus after 24 h	9	9	8

Data presented are mean value ± SD or number of patients, unless otherwise indicated. LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; PTCA = percutaneous transluminal coronary angioplasty; RCA = right coronary artery; r-hirudin = recombinant hirudin.

50 frames/s. After optical magnification, automatic gain and offset adjustment and digitization (512 × 512 pixels, eight bits), visual border recognition and tracing of the single worst view projection (i.e., that showing the most representative stenosis image) were performed. The traced vessel borders were stored, and the lesion variables and reference diameters were automatically computed.

Intracoronary thrombus was defined as an intraluminal filling defect surrounded on at least three sides with or without staining. *Angiographic success* was defined as diameter stenosis <50% immediately after coronary angioplasty.

Clinical events. Clinical events were documented until hospital discharge and were defined as follows: death, acute myocardial infarction, need for emergency coronary angioplasty or bypass graft surgery, recurrent chest pain and major and minor bleeding. *Major bleeding* was defined as either overt bleeding requiring transfusion or surgical intervention or intracranial bleeding. *Myocardial infarction* was defined as a more than twofold increase in creatine kinase (CK) levels above the upper limit of the reference site. *Recurrent angina* was defined as typical anginal chest pain at rest. Electrocardiograms were required on admission and after 24 and 48 h.

Laboratory investigations. Laboratory studies were performed to determine coagulation variables, including activated partial thromboplastin time as well as variables of myocardial cell necrosis (CK, troponin T). The activated partial thromboplastin time and variables of myocardial cell necrosis were measured before and directly after coronary angioplasty, as well as after 4, 8, 16, 24, 27 and 48 h. Other laboratory variables were measured on admission and after 24 and 48 h. Troponin T levels were assessed by enzyme-linked immunosorbent assay (27).

Statistical analysis. Graphical and descriptive methods were used to summarize the data and to present the results of the study. Quantitative data are expressed as mean value ± SD or as median (25%/75% percentiles). Statistical comparisons were based on the Fisher exact test (two-sided, alpha 5%) for the combined r-hirudin treatment groups versus the heparin group. The power of the study to detect a decrease in abnormal troponin T levels from 60% (heparin group) to 20% (combined r-hirudin groups) was 88%. The study was not designed to detect meaningful differences with regard to clinical outcome. A p value <0.05 was considered to indicate a significant difference. Data were stored on an HP 3000 data base. Statistical analyses were performed by means of PC-SAS software, version 6.04.

Results

Baseline patient characteristics are summarized in Table 1. Altogether, there were no significant differences among the three treatment groups. It was possible to perform safety analyses for all 61 patients and efficacy analyses for 59 (with respect to angiographic outcome). One patient (dosage group I) was excluded from the efficacy analysis because coronary angioplasty was not performed after randomization owing to the absence of a significant lesion; a coronary spasm had to be considered. Another patient (heparin group) had to be excluded because informed consent was withdrawn 5 h after commencement of treatment with the drugs under investigation.

Table 2. Adverse Events

	r-Hirudin			
	Dosage Group I (n = 21)	Dosage Group II (n = 19)	Heparin Group (n = 21)	p Value
Adverse cardiac events				
Serious				
Death	1 (4.8%)*		1 (4.8%)	
Myocardial infarction	1 (4.8%)	1 (5.3%)		
Acute coronary occlusion	1 (4.8%)		3 (14.3%)	
PTCA/stent	1 (4.8%)		2 (9.5%)	
CABG			1 (4.8%)	
Total pts affected	1 (4.8%)	1 (5.3%)	3 (14.3%)	0.33
Minor				
Recurrent chest pain		2 (10.5%)		
ECG ST segment change	3 (14.3%)	2 (10.5%)	3 (14.3%)	
Total pts affected	3 (14.3%)	2 (10.5%)	3 (14.3%)	1.0
Bleeding complications				
Major		1 (5.3%)		
Minor	2 (9.5%)		3 (14.3%)	
Total pts affected	2 (9.5%)	1 (5.3%)	3 (14.3%)	0.41

*Sudden death on day 11 due to reinfarction. Data presented are number (%) of patients (pts). CABG = coronary artery bypass graft surgery; ECG = electrocardiographic; other abbreviations as in Table 1.

Angiographic results. The number of attempted lesions, lesion location, severity of the lesions and other lesion variables were comparable in the treatment groups. Angiographic success was achieved in all patients in dosage groups I and II and in 18 of 20 patients in the heparin group (Table 1). No significant differences were found in the preangioplasty and postangioplasty incidence of intracoronary thrombus formation (Table 1).

Serious adverse cardiac events. In dosage group I, one patient had an abrupt coronary occlusion during coronary angioplasty, with subsequent transmural myocardial necrosis (Table 2). On day 11, the patient died suddenly after reinfarction. In dosage group II, one patient experienced a myocardial infarction on day 4. In the heparin group, one patient experienced an abrupt coronary occlusion during coronary angioplasty that necessitated emergency bypass graft surgery. This patient died on day 2 of extensive infarction with refractory cardiogenic shock. Two patients experienced abrupt coronary occlusion after coronary angioplasty that was successfully treated by stent implantation. Altogether, cardiac events were more frequent in the heparin group (three patients, 14.3%) than in the hirudin groups (one patient each in dosage group I [4.8%] and dosage group II [5.3%]). However, this difference was not statistically significant (p = 0.33).

Minor adverse cardiac events. Recurrent chest pain was observed in two patients (10.5%) in dosage group II (Table 2).

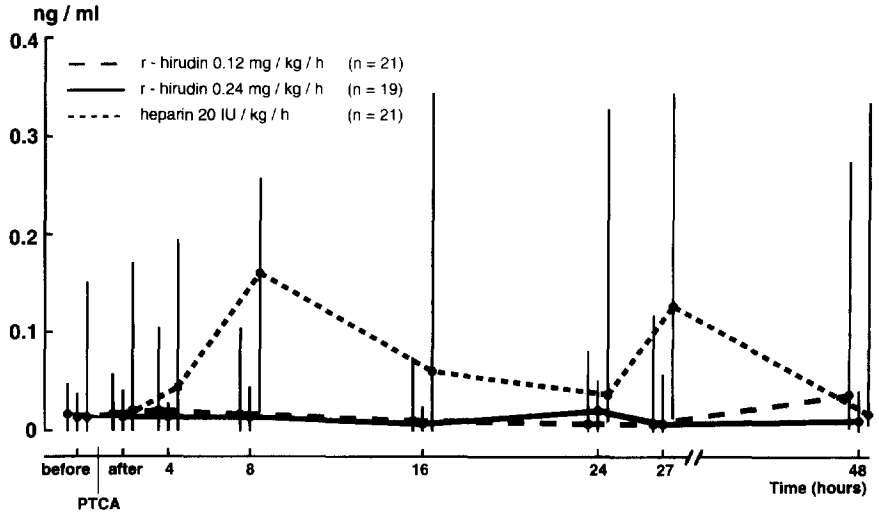

Figure 1. Troponin T concentrations (ng/ml) (medians **[circles]** with 25%/75% percentiles **[vertical lines]**). Upper limit 0.2 ng/ml.

Deterioration of the ST-T wave within 48 h of coronary angioplasty was observed in three patients (14.3%) in dosage group I, two (10.5%) in dosage group II and three (14.3%) in the heparin group (p = 1.0).

Bleeding complications. One major bleeding complication related to the catheter insertion site occurred in dosage group II and prompted transfusion of 2 U of blood (Table 2). There were two cases of minor bleeding at the puncture site in dosage group I and three in the heparin group (p = 0.41).

Markers of myocardial cell necrosis. We observed a significant increase in troponin T levels at 8 h after commencement of drug infusion in the heparin group (Fig. 1). Another peak was seen 27 h after the start of drug infusion (3 h after switching from the high to the low dose regimen). There was no comparable increase in troponin T levels in either of the hirudin groups (Fig. 1). A serum troponin T concentration >0.2 ng/ml was measured within 48 h of coronary angioplasty in 5 (25%) of 20 patients in dosage group I and 4 (22.2%) of 18 in dosage group II. Altogether, 9 (23.7%) of 38 patients in the hirudin groups had elevated troponin T levels compared with 11 (57.9%) of 19 patients in the heparin group (p = 0.01). There was no peak and no significant difference with regard to CK enzyme activity between the treatment groups. A pathologic increase in CK enzyme activity was observed in only one patient in each treatment group.

Coagulation variables. Median prolongation of the activated partial thromboplastin time compared with baseline was found to be 1.9-fold (range 0.9 to 4.7) in dosage group I, 2.3-fold (range 1.6 to 3.6) in dosage group II and 3.0-fold (range 1.0 to 3.9) in the heparin group at 24 h.

Discussion

Role of hirudin. Angioplasty in unstable angina is subject to a higher rate of complications than in stable angina, mainly because of thrombin generation at the site of the lesion. Hirudin, a specific inhibitor of thrombin, has been shown in previous studies (19–26) to be highly effective in preventing arterial thrombosis. Hirudin is a direct thrombin inhibitor and, in contrast to heparin, does not require antithrombin III as a cofactor. It is active against clot-bound thrombin, whereas heparin predominantly inhibits soluble thrombin (28). Moreover, heparin-induced thrombin inhibition can be counteracted by platelet factor 4 and fibronectin (21,22,24,29–31). Hirudin is also an effective inhibitor of thrombin-induced platelet activation (32–34), an observation that suggests that hirudin might be superior to heparin in preventing thrombotic complications in patients with unstable angina undergoing coronary angioplasty.

Serious adverse events. Because of the small sample size, the present study did not have the power to show significant differences in clinical outcome, although there was a trend toward more serious adverse cardiac events in the heparin group. In a recent multicenter trial (31), hirulog was compared with heparin in coronary angioplasty; there was a trend toward fewer abrupt vessel occlusions in the hirulog-treated group. Recent trials (35,36) indicate that hirudin reduces the incidence of major adverse cardiac events after angioplasty in patients with unstable angina.

Troponin T release. Previous studies have shown (27,37) troponin T to have a high sensitivity and specificity for myocardial cell injury. For example, Hamm et al. (37) reported elevated troponin T levels in patients with acute angina at rest. Only a minority of these patients had elevated CK-MB activity. Recently Talasz et al. (38) reported a significant increase in troponin T levels in patients with side branch occlusion after coronary angioplasty. In coronary angioplasty without complications, there was no significant increase in plasma concentrations of troponin T (38,39).

Although there were no differences in patient characteristics and baseline troponin T concentrations between our treatment groups, we observed a peak in troponin T median values 8 and 27 h after the start of treatment in the heparin group but not in the hirudin groups. There was no comparable increase in CK activity. The data indicate that minor myocar-

dial cell necrosis is common after coronary angioplasty in patients with unstable angina, which is probably related to angioplasty-enhanced endothelial injury, with activation of the coagulation system and platelet activation leading to thrombotic occlusion of smaller side branches or peripheral embolization. Postmortem studies (4) have demonstrated that microinfarctions are common in patients with unstable angina as a result of fissuring of an atheromatous plaque, with subsequent episodic embolization. In addition, an intermittent critical flow reduction corresponding to the degree of thrombus formation might contribute to myocardial cell damage. As evidenced by the greater activated partial thromboplastin time prolongation in the heparin group during the first 24 h, this difference in our results cannot be related to insufficient anticoagulation in the heparin group.

Our results indicate that hirudin may have greater potential than heparin to prevent such early ischemic events after coronary angioplasty for unstable angina pectoris. Moreover, a second peak in troponin T concentration was observed after 27 h. Again, there was an increase in troponin T levels in the heparin group only. This increase may be related to a rebound phenomenon after cessation or reduction of the heparin dose. A rebound phenomenon leading to myocardial infarction or recurrent chest pain after stopping heparin therapy has been observed by Theroux et al. (40) and Granger et al. (41). Gold et al. (42) reported rebound thrombin generation with an early dose-related recurrence of unstable angina after cessation of brief-duration therapy (4 h) with the specific thrombin inhibitor argatroban. Conversely, Topol et al. (25) did not find a rebound phenomenon after stopping hirudin therapy.

Bleeding complications. In previous trials (43,44), a trend toward an excess of hemorrhagic stroke was observed in patients receiving hirudin compared with those receiving heparin. We observed only one major bleeding event related to the catheter insertion site in 40 hirudin-treated patients. However, the number of patients in our study was too small for definite risk assessment of bleeding complications.

A prolonged activated partial thromboplastin time was associated with an increased risk of major hemorrhage in both heparin- and hirudin-treated patients in the Thrombolysis in Myocardial Infarction 9A trial (45). These data confirm the findings of our study, demonstrating greater antithrombotic efficacy with hirudin than heparin at a lower activated partial thromboplastin time level.

Conclusions. Our results support the postulated efficacy of r-hirudin in preventing myocardial ischemia after coronary angioplasty for unstable angina pectoris. Hirudin has the potential to provide more complete and potent antithrombotic action than heparin during and after coronary angioplasty, possibly at a lower activated partial thromboplastin time level than that required for the same antithrombotic effect of heparin. No safety risks, particularly in terms of bleeding, were manifested during the course of the present study.

Appendix

Study Co-Investigators

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